PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PS220507-142	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/NZ2005/000052	International filing date *(day/month/year)* 22 March 2005	Priority date *(day/month/year)* 22 March 2004

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

See Supplemental Sheet

Applicant

KIWI INGENUITY LIMITED et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **33** sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[X]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23 December 2005	22 June 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **KATHERINE MOERMAN** Telephone No. (02) 6283 2714

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NZ2005/000052

Box No. I Basis of the report

1. With regard to the **language,** this report is based on: .

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages as originally filed/furnished
pages* **5-18** received by this Authority on **3 January 2006** with the letter of **23 December 2005**
pages* **3, 4** received by this Authority on **15 May 2006** with the letter of **15 May 2006**

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **76-92** received by this Authority on **15 May 2006** with the letter of 15 May 2006
pages* received by this Authority on with the letter of

[X] the drawings:

pages **1-10** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: **1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part)**

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*

☒ no international search report has been established for said claim Nos. **1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part)**

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 6, 7, 27-35, 47, 48, 65-73, 92, 93, 95, 99-101 (fully) 1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part)	**YES**
	Claims	**NO**
Inventive step (IS)	Claims 6, 7, 27-35, 47, 48, 65-73, 92, 93, 95, 99-101 (fully) 1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part)	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims 1-108	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The claims of the present application are directed to synthetic molecules of the structure F-S1-S2-L (Claims 1-35 and 74), synthetic methods for the synthesis of such molecules (Claims 36-73), methods of effecting change in the surface antigens using such molecules (Claims 75-89), cells and multicellular structures incorporating such molecules (90-93), kits (Claims 94-101), and pharmaceutical preparations (Claims 102-108). The synthetic molecules of the present application are able to incorporate into lipid bi-layers, such as cell membranes, when a solution of the molecule is contacted with such a bi-layer and effect qualitative or quantitative changes in the surface antigens of that bi-layer.

The following documents, cited in the International Search Report have been considered for the purposes of this report:

D1 WO 2001/091805
D2 Massaguer, A. et al., Journal of Liposome Research (2001), 11(1), 103-113
D3 Ishida, Osamu et al., Pharmaceutical Research (2001), 18(7), 1042-1048
D4 Haselgrübler, Thomas et al., Bioconjugate Chemistry (1995), 6(3), 242-8
D5 Blume, G. et al., Biochimica et Biophysica Acta (1993), 1149(1), 180-4

D1 discloses synthetic molecules which comprise a peptide chain linked to a phospholipid moiety (compounds of general formula IIa) and specifically DPPE-GLU-GTKPPR, DPPG-GLU-GTKPPR, DPPA-GLU-GTKPPR in example 4 and DPPE-GLU-[di(aminodioxaoctanoyl)]-TLPPR-OH in example 23. These compounds are used as film-forming surfactants for producing liposomes for the delivery of contrast agents (page 28) or therapeutically active substances (page 34 from line 28).

D2 discloses molecules which have the peptide sequence GGRGRS incorporated onto the surface of liposomes through N-glutaryl dipalmitoyl phosphatidyl ethanolamine (NGPE) (page 105-106).

D3 discloses liposomes in which transferrin is coupled to the distal terminals of PEG chains (page 1043).

D4 discloses the molecule PDP-NH-PEG-NH-DMPE (scheme 1) and its conjugation to antibodies for use in the preparation of immunoliposomes and the anchorage of membranes or cells to surfaces.

D5 discloses PEG-modified liposomes in which Glu-plasminogen is coupled to di-stearyl phosphatidyl ethanolamine (NSPE) – PEG77 COOH (page 181 first column). In D2-D5 the peptide or protein is conjugated to the liposome after the liposome is formed.

The molecules disclosed in these citations are distinguished by the molecules of the present application as F is limited to being a carbohydrate. Claims 1- 35 are therefore novel and inventive in the light of D1-D5. Claims 36-74 are novel and inventive in the light of D1-D5 because these citations do not disclose or suggest the particular activators as defined within Claim 36. Claims 75-108 are novel and inventive in the light of D1-D5 because these citations do not disclose or suggest the particular uses and compositions as defined within these claims.

The subject matter defined in the claims of the present application is considered to be industrially applicable.

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 2004/045583	3 June 2004	12 November 2003	15 November 2002

WO 2004/045583 was published after the priority date after the present application and has not been considered for the purposes of novelty and inventiveness. However, this document may become relevant in the national phase of the application. Specifically, WO 2004/045583 discloses a molecule comprising a polyalkylene glycol bound to albumin for use in the preparation of liposomes which falls within the scope of the generic formulae of the present application.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

i) Claim 1 seeks to define a "synthetic membrane anchor or synthetic molecule construct" and this is construed as being directed to the molecules *per se*. Claim 1 is not restricted by activity. Any compounds that fall within the scope of the structure of the molecule defined within Claim 1 (and dependent claims) are considered to be highly relevant to the novelty and inventiveness of that claim.

ii) Claims 1-5 and 8-26 are not fully supported by the description with respect to the definitions of F, S1, S2 and L. The application provides support only for a small range of molecules as disclosed in the examples.

iii) Claim 24 is of indefinite scope because it is not readily apparent what the phrase "mediates a cell-solute interaction" includes.

iv) Claims 9 and 10 are not fully supported by the description as the phrases "spontaneously incorporates into a lipid bilayer when a solution of the synthetic molecule construct is contacted with the lipid bi-layer" and "stably incorporates into the lipid bilayer" seek to define the structure of the synthetic molecule construct by the activity of that molecule.

v) Claims 19 and 21-26 are not fully supported by the description because these claims define S1-S2 or F according to the activity that these sub-units confer on the molecule as a whole. It is considered that the scope of these claims covers areas which are not recognized by the applicant and includes mere speculation of possibilities that have not yet been explored.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Cover Sheet

C07F 9/117 (2006.01)
A61K 31/685 (2006.01)
A61K 31/7032 (2006.01)
A61P 43/00 (2006.01)
C07F 9/10 (2006.01)
C07H 15/04 (2006.01)
C12N 5/08 (2006.01)

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: III

Claims 1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part) are not fully supported by the description. Claims 1-5 and 8-26 include within their scope a cast number of compounds because of the broad definitions of F, S1, S2 and L. The International Searching Authority did not comprehensively search the full scope of the claims and the search was restricted to the compounds as exemplified in the examples and defined within claims 6, 7 and 27-35. Consequently, opinion regarding the novelty and inventiveness of the present application has been established with respect to Claims 6, 7, 27-35, 47, 48, 65-73, 92, 93, 95, 99-101 (fully) and Claims 1-5, 8-26, 36-46, 49-64, 74-91, 94, 96-98, 102-108 (in part).

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with the object to at least provide the public with a useful choice.

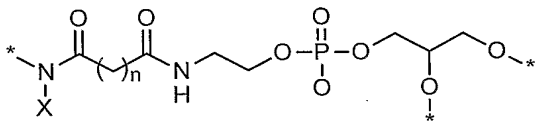
STATEMENTS OF INVENTION

In a **first** aspect the invention consists in a synthetic membrane anchor or synthetic molecule construct of the structure F-S_1-S_2-L where:

F is selected from the group consisting of carbohydrates;
S_1-S_2 is a spacer linking F to L; and
L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids, and sphingosine derived diacyl- and dialkyl-lipids, including ceramide.

Preferably L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids. More preferably L is selected from the group consisting of: diacylglycerolipids, phosphatidate, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, and diphosphatidyl glycerol derived from one or more of *trans*-3-hexadecenoic acid, *cis*-5-hexadecenoic acid, *cis*-7-hexadecenoic acid, *cis*-9-hexadecenoic acid, *cis*-6-octadecenoic acid, *cis*-9-octadecenoic acid, *trans*-9-octadecenoic acid, *trans*-11-octadecenoic acid, *cis*-11-octadecenoic acid, *cis*-11-eicosenoic acid or *cis*-13-docsenoic acid. More preferably the lipid is derived from one or more *cis*-destaurated fatty acids. Most preferably L is selected from the group consisting of: 1,2-O-dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE), 1,2-O-distearyl-sn-glycero-3-phosphatidylethanolamine (DSPE) and *rac*-1,2-dioleoylglycerol (DOG).

Preferably L is a glycerophospholipid and the molecule includes the substructure:



where n = 3 to 5, X is H or C, and * is other than H. Preferably n is 3.

Preferably the molecule is water soluble.

Preferably the molecule spontaneously incorporates into a lipid bi-layer when a solution of the molecule is contacted with the lipid bi-layer. More preferably the molecule stably incorporates into the lipid bilayer.

Preferably F, S_1, S_2 and L are covalently linked.

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Preferably F is selected from the group consisting of naturally occurring or synthetic glycotopes.

S_1-S_2 is selected to provide a water soluble synthetic membrane anchor or synthetic molecule construct.

In a first embodiment F is a naturally occurring or synthetic glycotope. Preferably F is a naturally occurring or synthetic glycotope consisting of three (trisaccharide) or more sugar units. More preferably F is a glycotope selected from the group consisting of lacto-neo-tetraosyl, lactotetraosyl, lacto-nor-hexaosyl, lacto-iso-octaosyl, globoteraosyl, globo-neo-tetraosyl, globopentaosyl, gangliotetraosyl, gangliotriaosyl, gangliopentaosyl, isoglobotriaosyl, isoglobotetraosyl, mucotriaosyl and mucotetraosyl series of oligosaccharides. Most preferably F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc.

When F is a glycotope, L is a glycerophospholipid and S_2 is selected from the group including: $-CO(CH_2)_3CO-$, $-CO(CH_2)_4CO-$ (adipate), $-CO(CH_2)_5CO-$ and $-CO(CH_2)_5NHCO(CH_2)_5CO-$, preferably S_1 is a C_{3-5}-aminoalkyl selected from the group consisting of: 3-aminopropyl, 4-aminobutyl, or 5-aminopentyl. More preferably S_1 is 3-aminopropyl.

In a second embodiment F is a molecule that mediates a cell-cell or cell-surface interaction. Preferably F is a carbohydrate with an affinity for a component expressed on a targeted cell or surface. More preferably F has an affinity for a component expressed on epithelial cells or extra-cellular matrices. Yet more preferably F has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium. Most preferably the component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

In a third embodiment F is a molecule that mediates a cell-solute interaction. Preferably F is a ligand for a binding molecule where the presence of the binding molecule is diagnostic for a pathological condition. More preferably F is a ligand for an antibody (immunoglobulin).

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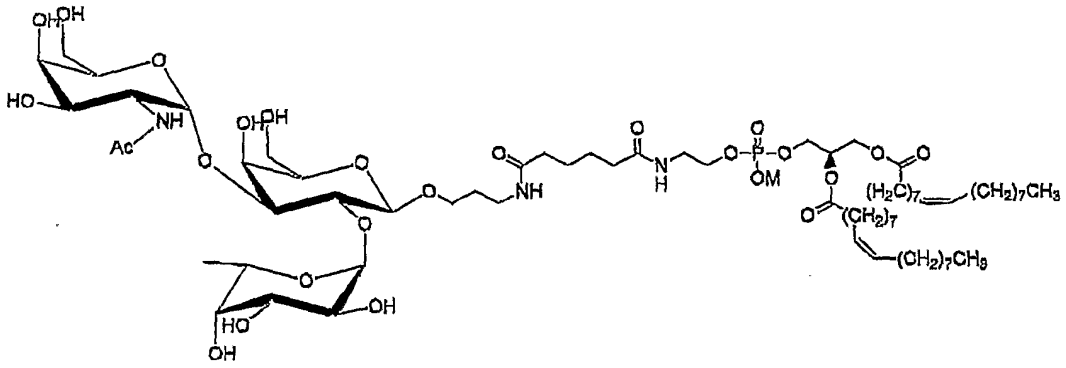
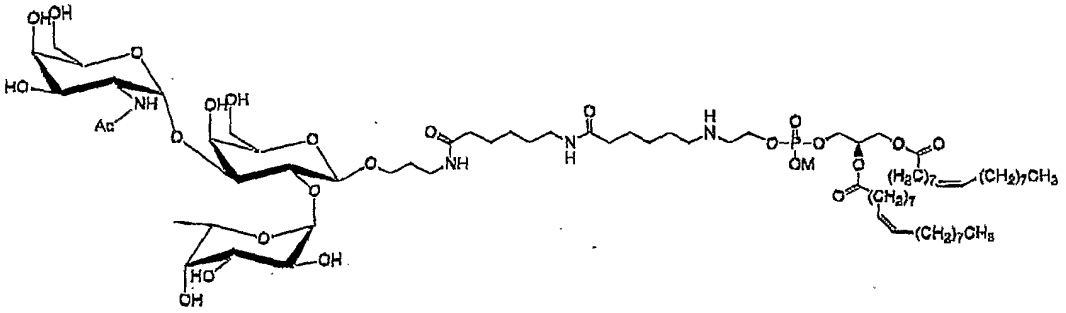
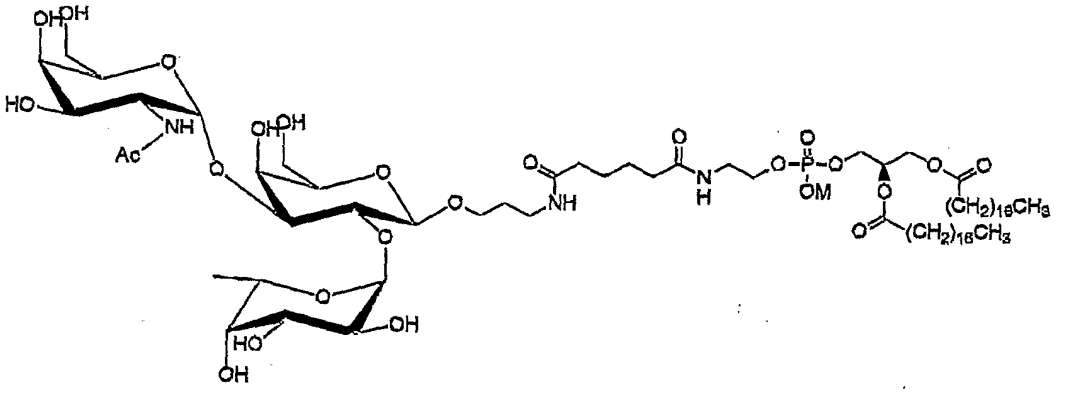
In specific embodiments the water soluble synthetic membrane anchor or synthetic molecule construct has the structure:



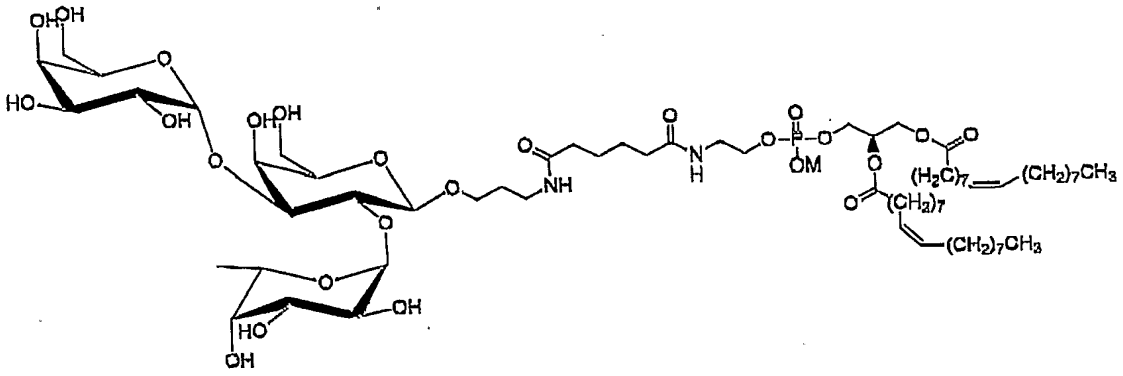
designated A_{tri}-sp-Ad-DOPE (I); the structure:



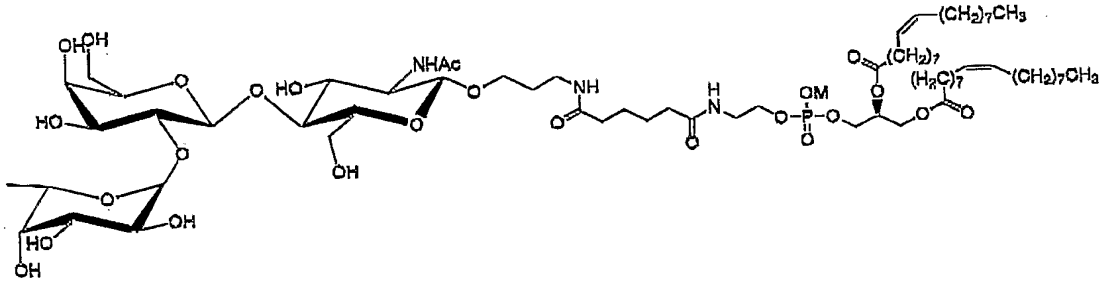
designated A_{tri}-sp$_1$-Ad-DOPE (II); the structure:



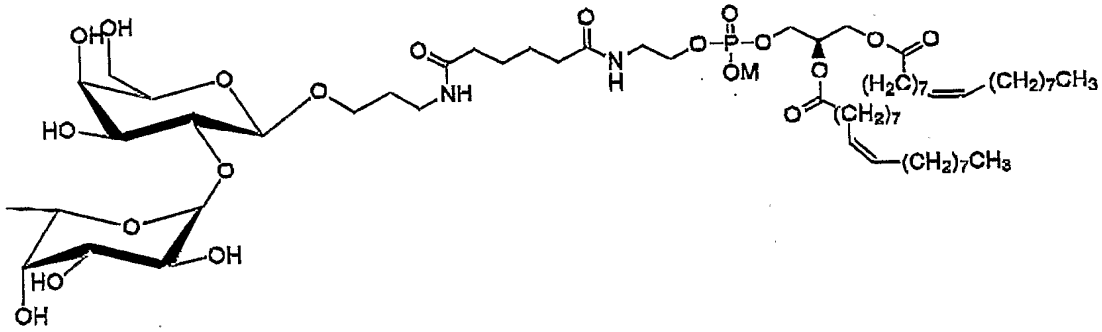
designated A_{tri}-sp-Ad-DSPE (III); the structure



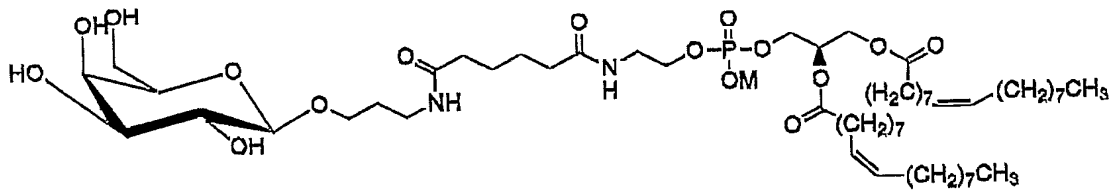
designated B_{tri}-sp-Ad-DOPE (**VI**); the structure:



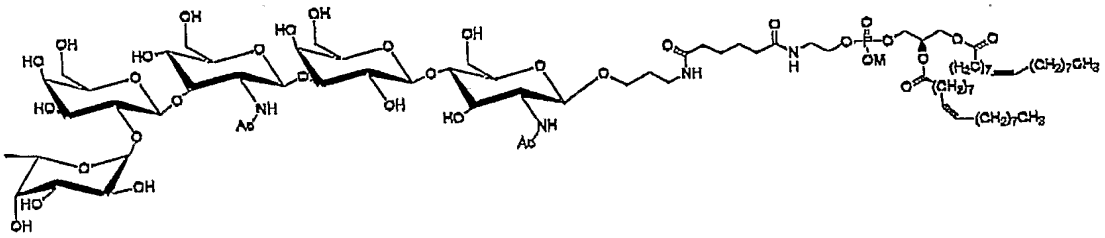
designated H_{tri}-sp-Ad-DOPE (**VII**); the structure:



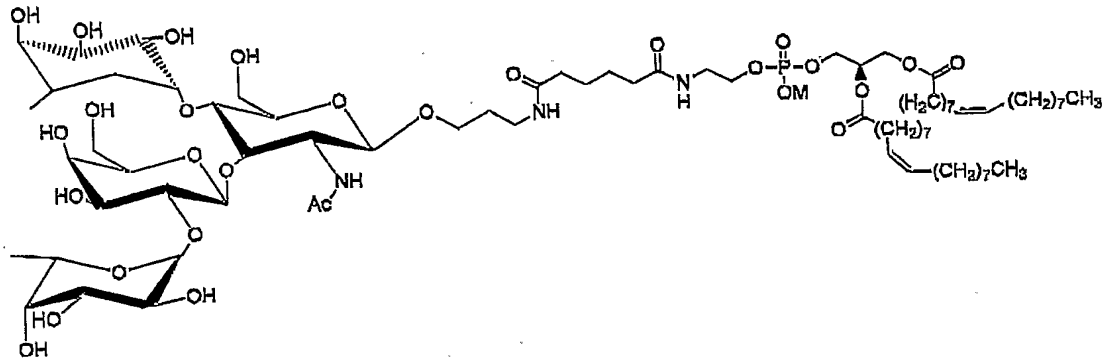
designated H_{di}-sp-Ad-DOPE (**VIII**); the structure:



designated $Gal\beta_1$-sp-Ad-DOPE (**IX**); the structure:



designated Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); or the structure:



designated Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

In a **second** aspect the invention consists in a method of preparing a synthetic membrane anchor or synthetic molecule construct of the structure F-S_1-S_2-L including the steps:

1. Reacting an activator (A) with a lipid (L) to provide an activated lipid (A-L);
2. Derivatising an antigen (F) to provide a derivatised antigen (F-S_1); and
3. Condensing A-L with F-S_1 to provide the molecule;

where:

A is an activator selected from the group including: *bis*(N-hydroxysuccinimidyl), *bis*(4-nitrophenyl), *bis*(pentafluorophenyl), *bis*(pentachlorophenyl) esters of carbodioic acids (C_3 to C_7);

L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids, and sphingosine derived diacyl- and dialkyl-lipids, including ceramide.

F is selected from the group consisting of carbohydrates; and

S_1-S_2 is a spacer linking F to L where S_1 is selected from the group including: primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine; and S_2 is absent or selected from the group including: -$CO(CH_2)_3CO$-, -$CO(CH_2)_4CO$- (adipate),

and $-CO(CH_2)_5CO-$.

Preferably the molecule is water soluble.

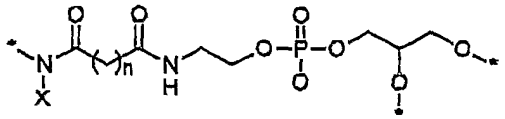
Preferably the molecule spontaneously incorporates into a lipid bi-layer when a solution of the molecule is contacted with the lipid bi-layer. More preferably the molecule stably incorporates into the lipid bilayer.

Preferably F, S_1, S_2 and L are covalently linked.

Preferably F is selected from the group consisting of naturally occurring or synthetic glycotopes.

Preferably L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids. More preferably L is selected from the group consisting of: diacylglycerolipids, phosphatidate, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, and diphosphatidyl glycerol derived from one or more of *trans*-3-hexadecenoic acid, *cis*-5-hexadecenoic acid, *cis*-7-hexadecenoic acid, *cis*-9-hexadecenoic acid, *cis*-6-octadecenoic acid, *cis*-9-octadecenoic acid, *trans*-9-octadecenoic acid, *trans*-11-octadecenoic acid, *cis*-11-octadecenoic acid, *cis*-11-eicosenoic acid or *cis*-13-docsenoic acid. More preferably the lipid is derived from one or more *cis*-destaurated fatty acids. Most preferably L is selected from the group consisting of: 1,2-O-dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE), 1,2-O-distearyl-sn-glycero-3-phosphatidylethanolamine (DSPE) and *rac*-1,2-dioleoylglycerol (DOG).

Preferably L is a glycerophospholipid and the molecule includes the substructure:



where n = 3 to 5, X is H or C, and * is other than H. Preferably n is 3.

Preferably A ($R-S_2$) and S_1 are selected to provide a water soluble synthetic molecule construct.

In a first embodiment F is a naturally occurring or synthetic glycotope. Preferably F is a naturally occurring or synthetic glycotope consisting of three (trisaccharide) or more sugar units. More preferably F is a glycotope selected from the group consisting of lacto-neo-tetraosyl, lactotetraosyl, lacto-nor-hexaosyl, lacto-iso-octaosyl, globoteraosyl, globo-neo-tetraosyl, globopentaosyl, gangliotetraosyl, gangliotriaosyl, gangliopentaosyl, isoglobotriaosyl,

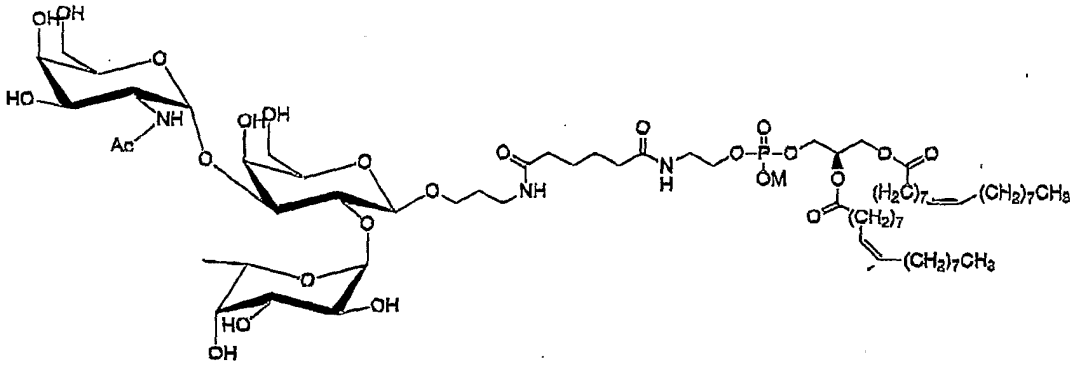
isoglobotetraosyl, mucotriaosyl and mucotetraosyl series of oligosaccharides. Most preferably F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc.

When F is a glycotope, L is a glycerophospholipid and S_2 is selected from the group including: -$CO(CH_2)_3CO$-, -$CO(CH_2)_4CO$- (adipate), -$CO(CH_2)_5CO$- and -$CO(CH_2)_5NHCO(CH_2)_5CO$-, preferably S_1 is a C_{3-5}-aminoalkyl selected from the group consisting of: 3-aminopropyl, 4-aminobutyl, or 5-aminopentyl. More preferably S_1 is 3-aminopropyl.

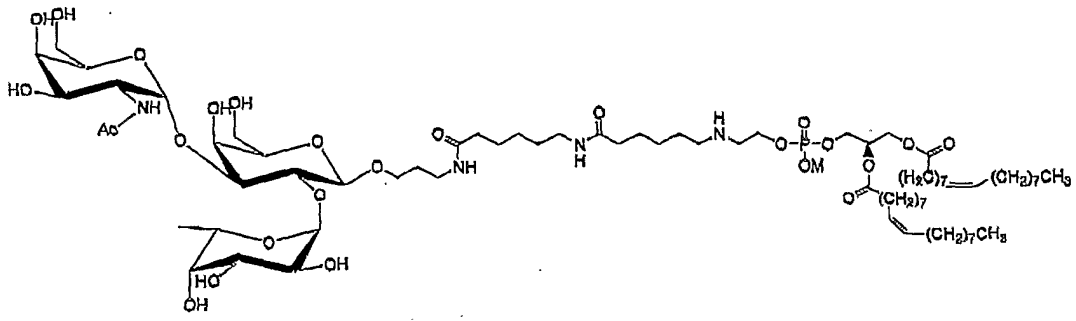
In a second embodiment F is a molecule that mediates a cell-cell or cell-surface interaction. Preferably F is carbohydrate with an affinity for a component expressed on a targeted cell or surface. More preferably F has an affinity for a component expressed on epithelial cells or extra-cellular matrices. Yet more preferably F has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium. Most preferably the component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

In a third embodiment F is a molecule that mediates a cell-solute interaction. Preferably F is a ligand for a binding molecule where the presence of the binding molecule is diagnostic for a pathological condition. More preferably F is a ligand for an antibody (immunoglobulin).

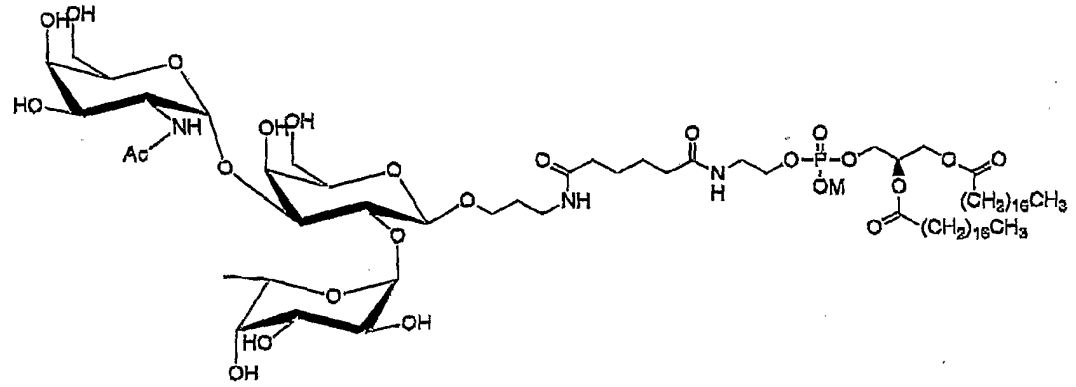
In specific embodiments the water soluble synthetic molecule construct has the structure:



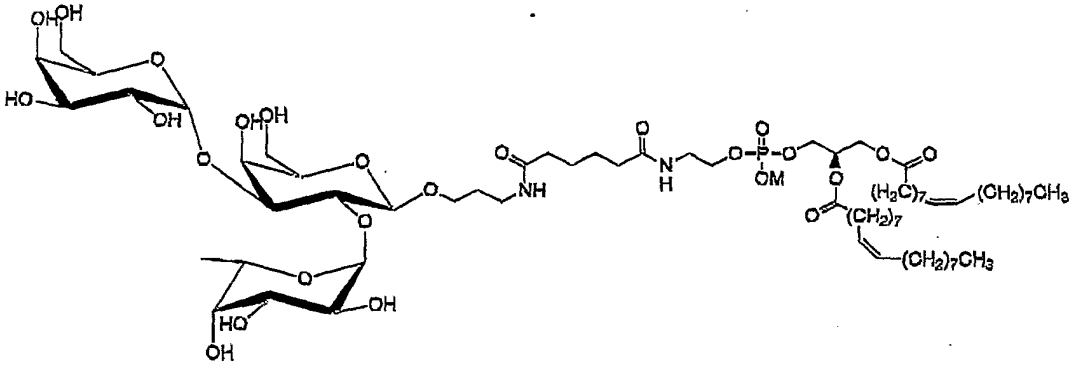
designated A_{IN}-sp-Ad-DOPE (I); the structure:



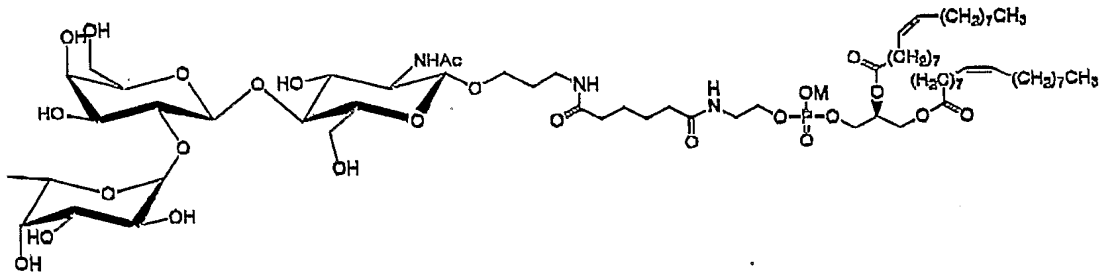
designated A_{tri}-spsp$_1$-Ad-DOPE (II); the structure:



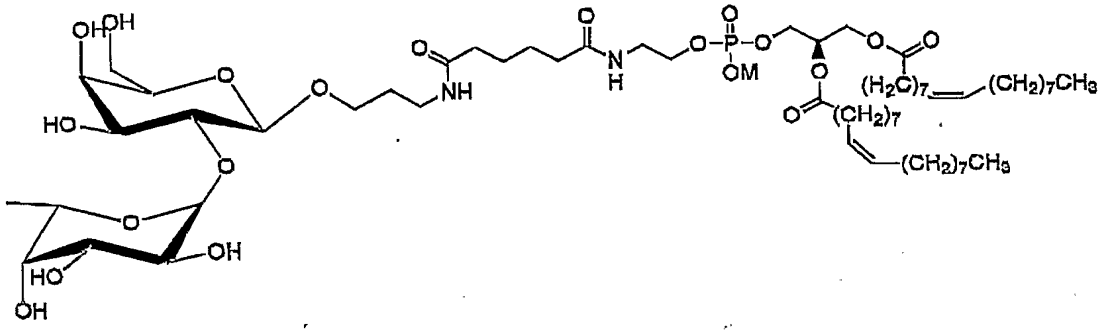
designated A_{tri}-sp-Ad-DSPE (III); the structure



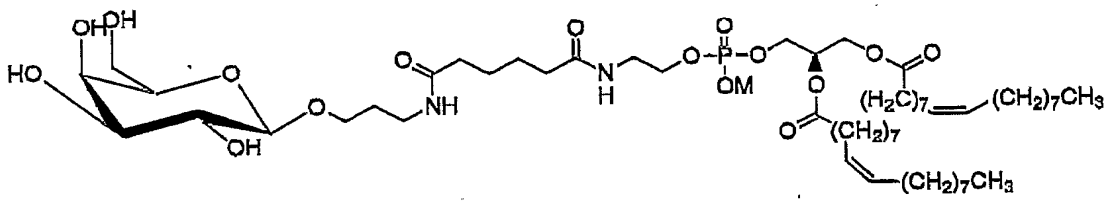
designated B_{tri}-sp-Ad-DOPE (VI); the structure:



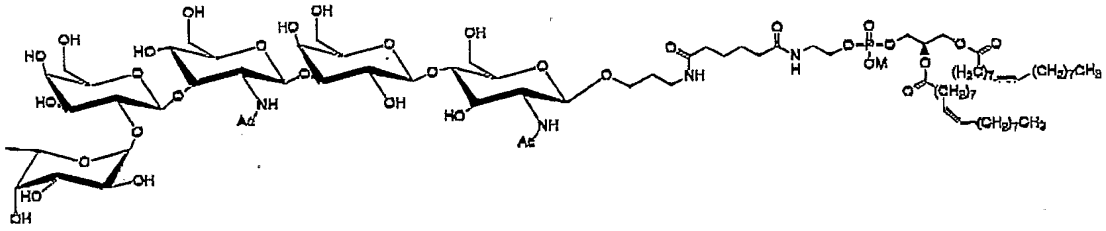
designated $H_{(tr)}$-sp-Ad-DOPE (**VII**); the structure:



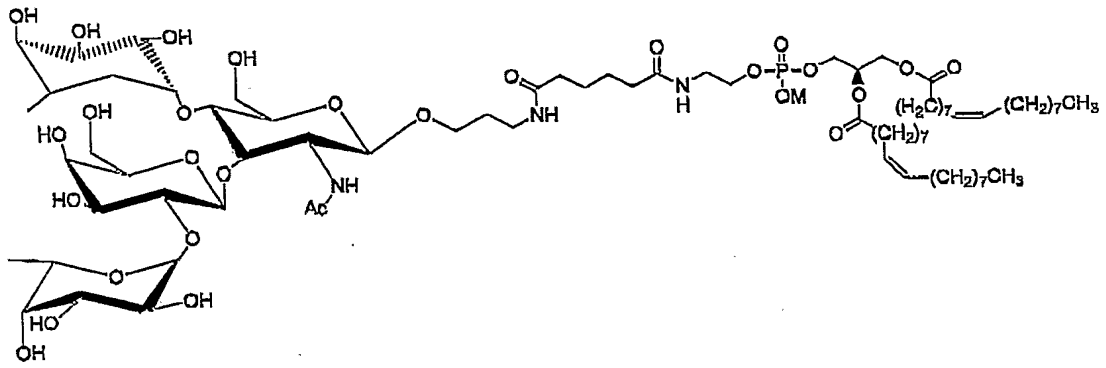
designated $H_{(di)}$-sp-Ad-DOPE (**VIII**); the structure:



designated Galß$_{(i)}$-sp-Ad-DOPE (**IX**); the structure:



designated Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); or the structure:



designated Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

In a **third** aspect the invention consists in a water soluble synthetic membrane anchor or synthetic molecule construct prepared by a method according to the second aspect of the invention.

In a **fourth** aspect the invention consists in a method of effecting qualitative and/or quantitative changes in the surface antigens expressed by a cell or multi-cellular structure including the step:

1. Contacting a suspension of the cell or multi-cellular structure with a synthetic membrane anchor or synthetic molecule construct according to the first aspect or third aspect of the invention for a time and at a temperature sufficient to effect the qualitative and/or quantitative change in the surface antigens expressed by the cell or multi-cellular structure.

Preferably the cell or multi-cellular structure is of human or murine origin.

Preferably the concentration of the water soluble synthetic membrane anchor or synthetic molecule construct in the suspension is in the range 0.1 to 10 mg/mL.

Preferably the temperature is in the range 2 to 37 °C. More preferably the temperature is in the range 2 to 25 °C. Most preferably the temperature is in the range 2 to 4 °C.

In a first embodiment the cell is a red blood cell.

In this embodiment preferably F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-

3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc. More preferably F is selected from the group of glycotopes consisting of the oligosaccharides GalNAcα1-3(Fucα1-2)Galß and Galα1-3(Fucα1-2)Galß.

Preferably the synthetic molecule construct is selected from the group including: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

In a second embodiment the multi-cellular structure is an embryo.

In this embodiment preferably F is an attachment molecule where the attachment molecule has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium.

The component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

Preferably the synthetic membrane anchor or synthetic molecule construct is selected from the group including: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

In a third embodiment the cell is red blood cell.

In this embodiment preferably F is a ligand for a binding molecule where the presence of the binding molecule is diagnostic for a pathological condition. More preferably F is a ligand for an antibody (immunoglobulin).

In a **fifth** aspect the invention consists in a cell or multi-cellular structure incorporating a water soluble synthetic membrane anchor or synthetic molecule construct according to the first or third aspect of the invention.

Preferably the cell or multi-cellular structure is of human or murine origin.

In a first embodiment the cell is a red blood cell incorporating a water soluble synthetic membrane anchor or synthetic molecule construct selected from the group including: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

In a second embodiment the multi-cellular structure is an embryo incorporating a water soluble synthetic membrane anchor or synthetic molecule construct selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

In a **sixth** aspect the invention consists in a kit comprising a dried preparation or solution of a water soluble synthetic membrane anchor or synthetic molecule construct according to the first or third aspect of the invention.

Preferably the synthetic membrane anchor or water soluble synthetic molecule construct according to the first or third aspect of the invention is selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

In an **seventh** aspect the invention consists in a kit comprising a suspension in a suspending solution of cells or multi-cellular structures according to the fifth aspect of the invention.

Preferably the suspending solution is substantially free of lipid.

Preferably the cell or multi-cellular structure is of human or murine origin.

Preferably the cells are red blood cells that do not naturally express A- or B-antigen and incorporate a water soluble synthetic membrane anchor or synthetic molecule construct selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**). More preferably the cells are sensitivity controls.

In a **eighth** aspect the invention consists in a pharmaceutical preparation comprising a dried

preparation or solution of a water soluble synthetic membrane anchor or synthetic molecule construct according to the first or fourth aspect of the invention.

Preferably the pharmaceutical preparation is in a form for administration by inhalation.

Preferably the pharmaceutical preparation is in a form for administration by injection.

In an **ninth** aspect the invention consists in a pharmaceutical preparation comprising cells or multi-cellular structures according to the fifth aspect of the invention.

Preferably the cells or multi-cellular structures are of human or murine origin.

Preferably the pharmaceutical preparation is in a form for administration by inhalation.

Preferably the pharmaceutical preparation is in a form for administration by injection.

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[text continued from page 15]

DETAILED DESCRIPTION

The synthetic molecule constructs of the invention spontaneously and stably incorporate into a lipid bi-layer, such as a membrane, when a solution of the molecule is contacted with the lipid bi-layer. Whilst not wishing to be bound by theory it is believed that the insertion into the membrane of the lipid tails of the lipid (L) is thermodynamically favoured. Subsequent disassociation of the synthetic molecule construct from the lipid membrane is believed to be thermodynamically unfavoured. Surprisingly, the synthetic molecule constructs identified herein have also been found to be water soluble.

The synthetic molecule constructs of the invention are used to transform cells resulting in qualitative and/or quantitative changes in the surface antigens expressed. It will be recognised that the transformation of cells in accordance with the invention is distinguished from transformation of cells by genetic engineering. The invention provides for phenotypic transformation of cells without *genetic* transformation.

In the context of this description the term "transformation" in reference to cells is used to refer to the insertion or incorporation into the cell membrane of exogenously prepared synthetic molecule constructs thereby effecting qualitative and quantitative changes in the cell surface antigens expressed by the cell.

The synthetic molecule constructs of the invention comprise an antigen (F) linked to a lipid portion (or moiety) (L) via a spacer (S_1-S_2). The synthetic molecule constructs can be prepared by the condensation of a primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine derivative of the antigen with an activated lipid. Methods of preparing neoglycoconjugates have been reviewed (Bovin, N. Biochem. Soc. Symp., 69, 143-160).

A desired phenotypic transformation may be achieved using the synthetic molecule constructs

of the invention in a one step method or a two step method. In the one step method the water soluble synthetic molecule construct (F-S_1-S_2-L) comprises the surface antigen as F.

In the two step method the synthetic molecule construct (F-S_1-S_2-L) comprises an antigen (F) that serves as a functional group to which a surface antigen can be linked following insertion of the synthetic molecule construct into the membrane. When used in the two step method the synthetic molecule construct is acting as a synthetic membrane anchor.

In accordance with the invention the primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine and the activator of the lipid are selected to provide a synthetic molecule construct that is water soluble and will spontaneously and stably incorporate into a lipid bi-layer when a solution of the synthetic molecule construct is contacted with the lipid bi-layer.

In the context of this description the phrase "water soluble" means a stable, single phase system is formed when the synthetic molecule construct is contacted with water or saline (such as PBS) in the absence of organic solvents or detergents, and the term "solution" has a corresponding meaning.

In the context of this description the phrase "stably incorporate" means that the synthetic molecule constructs incorporate into the lipid bi-layer or membrane with minimal subsequent exchange between the lipid bi-layer or membrane and the external aqueous environment of the lipid bi-layer or membrane.

The selection of the primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine and the activator depends on the physico-chemical properties of the antigen (F) to be linked to the lipid (L).

It will be understood by those skilled in the art that for a non-specific interaction, such as the interaction between a diacyl- or dialkyl-glycerolipid and a membrane, structural and stereo-isomers of naturally occurring lipids can be functionally equivalent. For example, it is contemplated by the inventors that diacylglycerol 2-phosphate could be substituted for phosphatidate (diacylglycerol 3-phosphate). Furthermore it is contemplated by the inventors that the absolute configuration of phosphatidate can be either R or S.

The inventors have determined that to prepare synthetic molecule constructs of the invention where the antigen (F) is an oligosaccharide selected from the group of glycotopes for A-, B- and H-antigens of the ABO blood groups, the primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine, and the activator should be selected to provide a spacer (S_1-S_2) with a structure according to one of those presented here:

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CLAIMS:

(1) A **synthetic membrane anchor** or **synthetic molecule construct** of the structure F-S_1-S_2-L where:

- F is selected from the group consisting of carbohydrates;
- S_1-S_2 is a spacer linking F to L; and
- L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids, and sphingosine derived diacyl- and dialkyl-lipids, including ceramide.

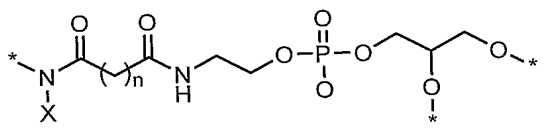
(2) The synthetic membrane anchor or synthetic molecule construct according to any one of claim 1 where L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids.

(3) The synthetic membrane anchor or synthetic molecule construct according to claims 1 or 2 where L is selected from the group consisting of: diacylglycerolipids, phosphatidate, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, and diphosphatidyl glycerol derived from one or more of *trans*-3-hexadecenoic acid, *cis*-5-hexadecenoic acid, *cis*-7-hexadecenoic acid, *cis*-9-hexadecenoic acid, *cis*-6-octadecenoic acid, *cis*-9-octadecenoic acid, *trans*-9-octadecenoic acid, *trans*-11-octadecenoic acid, *cis*-11-octadecenoic acid, *cis*-11-eicosenoic acid or *cis*-13-docsenoic acid.

(4) The synthetic membrane anchor or synthetic molecule construct according to claim 3 where the lipid is derived from one or more *cis*-destaurated fatty acids.

(5) The synthetic membrane anchor or synthetic molecule construct according to claim 4 where L is selected from the group consisting of: 1,2-O-dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE), 1,2-O-distearyl-sn-glycero-3-phosphatidylethanolamine (DSPE) and *rac*-1,2-dioleoylglycerol (DOG).

(6) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 5 where L is a glycerophospholipid and the synthetic molecule construct includes the substructure:



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where n = 3 to 5, X is H or C, and * is other than H.

(7) The synthetic membrane anchor or synthetic molecule construct according to claim 6 where n is 3.

(8) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 7 where the synthetic membrane anchor or synthetic molecule construct is water soluble.

(9) The synthetic membrane anchor or synthetic molecule construct according to claim 8 where the synthetic membrane anchor or synthetic molecule construct spontaneously incorporates into a lipid bi-layer when a solution of the synthetic membrane anchor or synthetic molecule construct is contacted with the lipid bi-layer.

(10) The synthetic membrane anchor or synthetic molecule construct according to claim 9 where the synthetic membrane anchor or synthetic molecule construct stably incorporates into the lipid bilayer.

(11) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 10 where F, S_1, S_2 and L are covalently linked.

(12) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 11 where F is selected from the group consisting of naturally occurring or synthetic glycotopes.

(13) The synthetic membrane anchor or synthetic molecule construct according to claim 12 where F is a naturally occurring or synthetic glycotope consisting of three (trisaccharide) or more sugar units.

(14) The synthetic membrane anchor or synthetic molecule construct according to claim 13 where F is a glycotope selected from the group consisting of lacto-neo-tetraosyl, lactotetraosyl, lacto-nor-hexaosyl, lacto-iso-octaosyl, globoteraosyl, globo-neo-tetraosyl, globopentaosyl, gangliotetraosyl, gangliotriaosyl, gangliopentaosyl, isoglobotriaosyl, isoglobotetraosyl, mucotriaosyl and mucotetraosyl series of oligosaccharides.

(15) The synthetic membrane anchor or synthetic molecule construct according to claim 14 where F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-

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6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc.

(16) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 15 where when F is a glycotope, L is a glycerophospholipid and S_2 is selected from the group including: $-CO(CH_2)_3CO-$, $-CO(CH_2)_4CO-$ (adipate), $-CO(CH_2)_5CO-$, and $-CO(CH_2)_5NHCO(CH_2)_5CO-$.

(17) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 16 where S_1 is a C_{3-5}-aminoalkyl selected from the group consisting of: 3-aminopropyl, 4-aminobutyl, or 5-aminopentyl.

(18) The synthetic membrane anchor or synthetic molecule construct according to claim 17 where S_1 is 3-aminopropyl.

(19) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 18 where F mediates a cell-cell or cell-surface interaction.

(20) The synthetic membrane anchor or synthetic molecule construct according to claim 19 where F is carbohydrate with an affinity for a component expressed on a targeted cell or surface.

(21) The synthetic membrane anchor or synthetic molecule construct according to claim 20 where F has an affinity for a component expressed on epithelial cells or extra-cellular matrices.

(22) The synthetic membrane anchor or synthetic molecule construct according to claim 21 where F has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium.

(23) The synthetic membrane anchor or synthetic molecule construct according to claim 22 where the component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

(24) The synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 18 where F mediates a cell-solute interaction.

(25) The synthetic membrane anchor or synthetic molecule construct according to claim 24 where F is a ligand for a binding molecule where the presence of the binding molecule is

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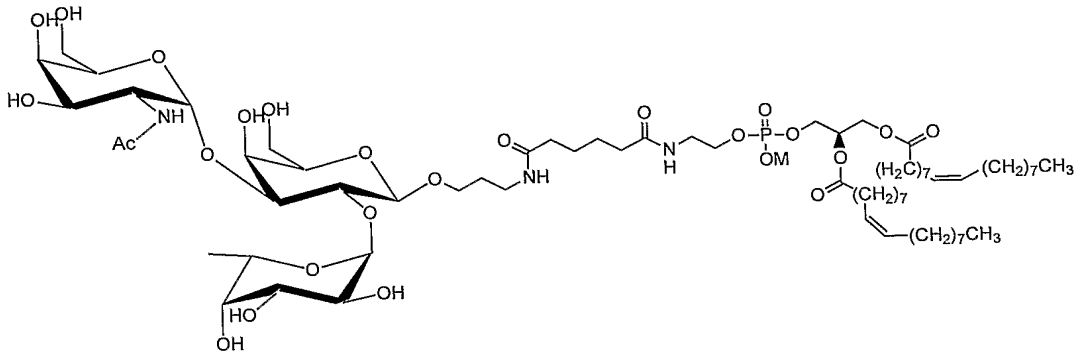
diagnostic for a pathological condition.

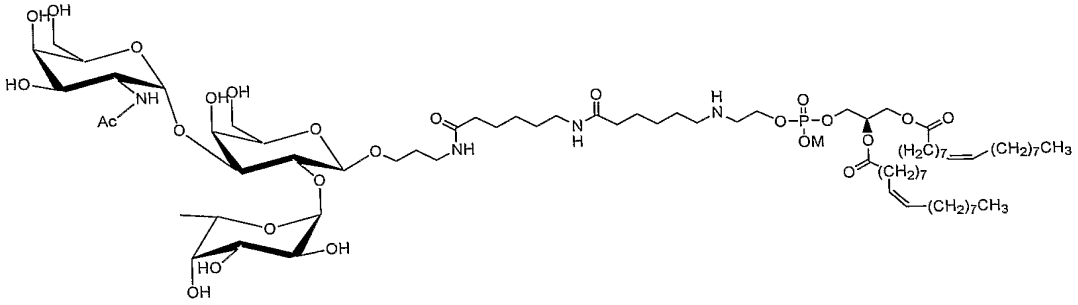
(26) The synthetic membrane anchor or synthetic molecule construct according to claim 25 where F is a ligand for an antibody (immunoglobulin).

(27) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated A_{tri}-sp-Ad-DOPE (**I**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(28) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated A_{tri}-spsp_1-Ad-DOPE (**II**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

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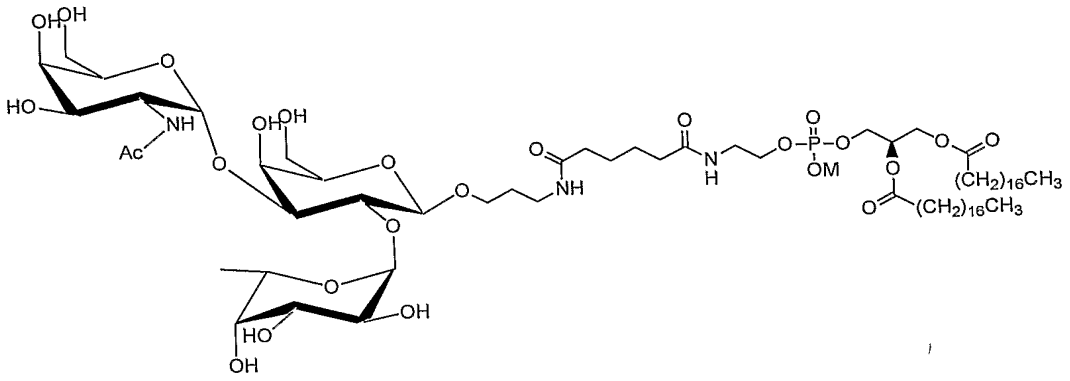
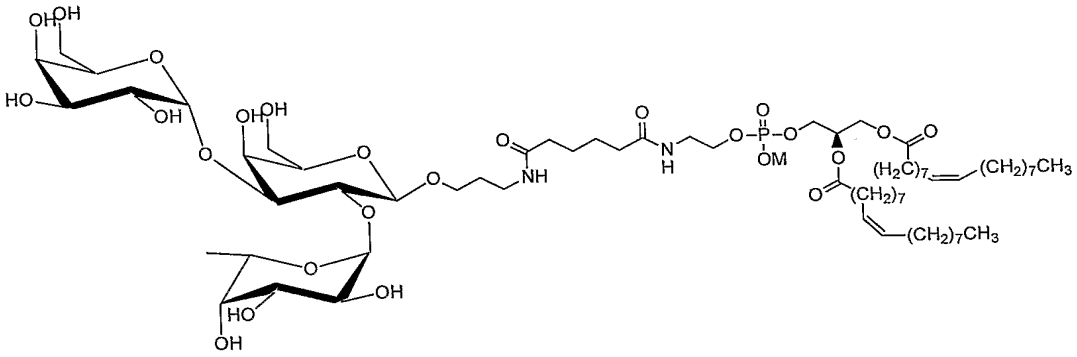
(29) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated A_{tri}-sp-Ad-DSPE (**III**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(30) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated B_{tri}-sp-Ad-DOPE (**VI**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

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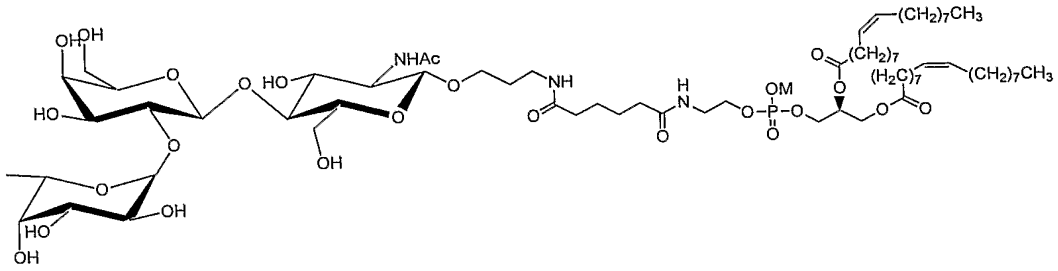
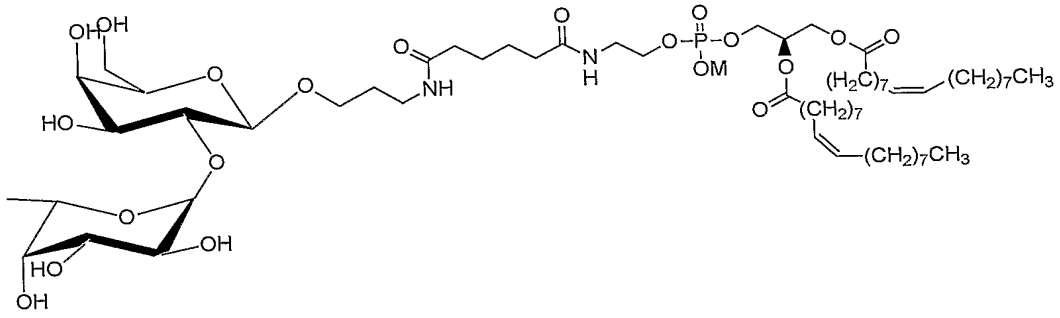
(31) A synthetic membrane anchor or synthetic molecule construct of the structure:



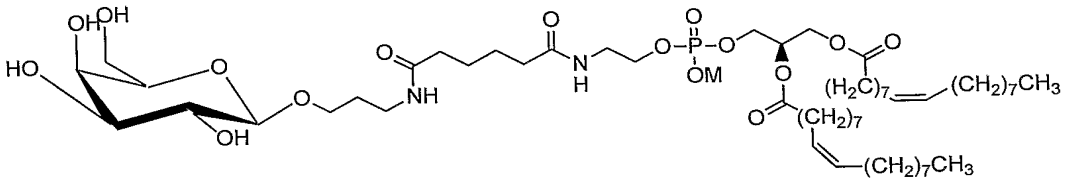
designated H_{tri}-sp-Ad-DOPE (**VII**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(32) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated H_{di}-sp-Ad-DOPE (**VIII**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(33) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated Galß$_i$-sp-Ad-DOPE (**IX**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

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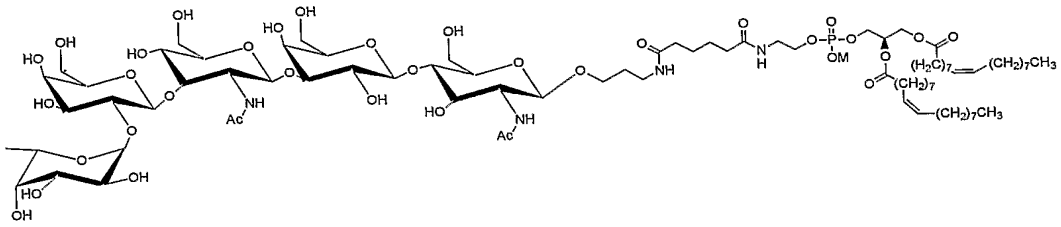
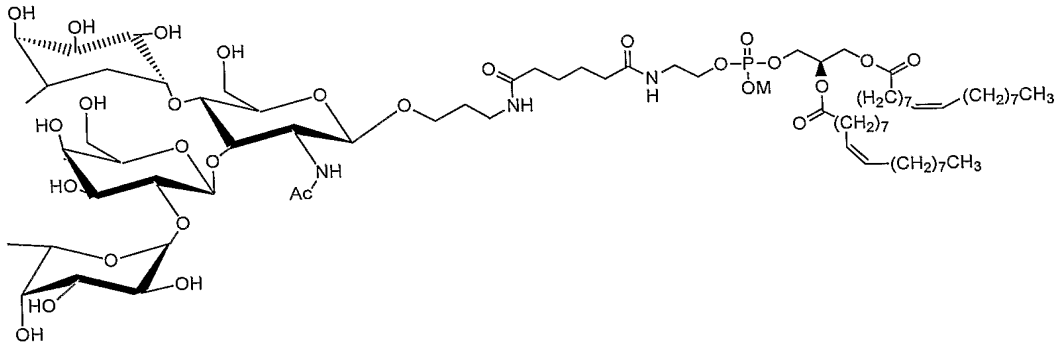
(34) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(35) A synthetic membrane anchor or synthetic molecule construct of the structure:



designated Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**) and M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(36) A **method** of preparing a synthetic membrane anchor or synthetic molecule construct of the structure F-S_1-S_2-L including the steps:

- Reacting an activator (A) with a lipid (L) to provide an activated lipid (A-L);
- Derivatising an antigen (F) to provide a derivatised antigen (F-S_1); and
- Condensing A-L with F-S_1 to provide the construct;

where:

A is an activator selected from the group including: *bis*(N-hydroxysuccinimidyl), *bis*(4-nitrophenyl), *bis*(pentafluorophenyl), *bis*(pentachlorophenyl) esters of carbodioic acids (C_3 to C_7);

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L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids, and sphingosine derived diacyl- and dialkyl-lipids, including ceramide.
F is selected from the group consisting of carbohydrates,; and
S_1-S_2 is a spacer linking F to L where S_1 is selected from the group including: primary aminoalkyl, secondary aliphatic aminoalkyl or primary aromatic amine; and S_2 is absent or selected from the group including: -$CO(CH_2)_3CO$-, -$CO(CH_2)_4CO$- (adipate), and -$CO(CH_2)_5CO$-.

(37) The method according to claim 36 where the synthetic membrane anchor or synthetic molecule construct is water soluble.

(38) The method according to claim 36 or 37 where the synthetic membrane anchor or synthetic molecule construct spontaneously incorporates into a lipid bi-layer when a solution of the synthetic membrane anchor or synthetic molecule construct is contacted with the lipid bi-layer.

(39) The method according to claim 38 where the synthetic molecule construct stably incorporates into the lipid bilayer.

(40) The method according to any one of claims 36 to 39 where F, S_1, S_2 and L are covalently linked.

(41) The method according to any one of claims 36 to 40 where F is selected from the group consisting of naturally occurring or synthetic glycotopes.

(42) The method according to claim 41 where F is selected from the group consisting of naturally occurring or synthetic glycotopes.

(43) The method according to any one of claims 36 to 42 where L is a lipid selected from the group consisting of diacyl- and dialkyl-glycerolipids, including glycerophospholipids.

(44) The method according to claim 43 where L is selected from the group consisting of: diacylglycerolipids, phosphatidate, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, and diphosphatidyl glycerol derived from one or more of *trans*-3-hexadecenoic acid, *cis*-5-hexadecenoic acid, *cis*-7-hexadecenoic acid, *cis*-9-hexadecenoic acid, *cis*-6-octadecenoic acid, *cis*-9-octadecenoic acid, *trans*-9-octadecenoic acid, *trans*-11-octadecenoic acid, *cis*-11-octadecenoic acid, *cis*-11-eicosenoic acid or *cis*-13-docsenoic acid.

(45) The method according to claim 44 where the lipid is derived from one or more *cis*-

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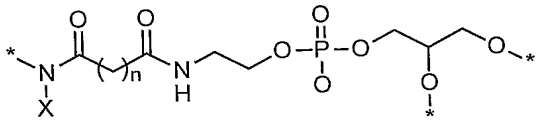
destaurated fatty acids.

(46) The method according to claim 45 where L is selected from the group consisting of: 1,2-O-dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE), 1,2-O-distearyl-sn-glycero-3-phosphatidylethanolamine (DSPE) and *rac*-1,2-dioleoylglycerol (DOG).

(47) The method according to any one of claims 36 to 46 where L is a glycerophospholipid and the synthetic molecule construct includes the substructure:



where n = 3 to 5, X is H or C, and * is other than H.

(48) The method according to claim 47 where n is 3.

(49) The method according to any one of claims 36 to 46 where A and S_1 are selected to provide a water soluble synthetic molecule construct.

(50) The method according to any one of claims 36 to 49 where F is a naturally occurring or synthetic glycotope.

(51) The method according to claim 50 where F is a naturally occurring or synthetic glycotope consisting of three (trisaccharide) or more sugar units.

(52) The method according to claim 50 where F is a glycotope selected from the group consisting of lacto-neo-tetraosyl, lactotetraosyl, lacto-nor-hexaosyl, lacto-iso-octaosyl, globoteraosyl, globo-neo-tetraosyl, globopentaosyl, gangliotetraosyl, gangliotriaosyl, gangliopentaosyl, isoglobotriaosyl, isoglobotetraosyl, mucotriaosyl and mucotetraosyl series of oligosaccharides.

(53) The method according to claim 50 where F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc.

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(54) The method according to any one of claims 36 to 53 where when F is a glycotope, L is a glycerophospholipid and S_2 is selected from the group including: $-CO(CH_2)_3CO-$, $-CO(CH_2)_4CO-$ (adipate), $-CO(CH_2)_5CO-$ and $-CO(CH_2)_5NHCO(CH_2)_5CO-$.

(55) The method according to any one of claims 36 to 54 where S_1 is a C_{3-5}-aminoalkyl selected from the group consisting of: 3-aminopropyl, 4-aminobutyl, or 5-aminopentyl.

(56) The method according to claim 55 where S_1 is 3-aminopropyl.

(57) The method according to any one of claims 36 to 49 where F mediates a cell-cell or cell-surface interaction.

(58) The method according to claim 57 where F is a carbohydrate with an affinity for a component expressed on a targeted cell or surface.

(59) The method according to claim 58 where F has an affinity for a component expressed on epithelial cells or extra-cellular matrices.

(60) The method according to claim 59 where F has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium.

(61) The method according to claim 60 where the component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

(62) The method according to any one of claims 36 to 49 where F is a synthetic molecule construct that mediates a cell-solute interaction.

(63) The method according to claim 62 where F is a ligand for a binding molecule where the presence of the binding molecule is diagnostic for a pathological condition.

(64) The method according to claim 63 where F is a ligand for an antibody (immunoglobulin).

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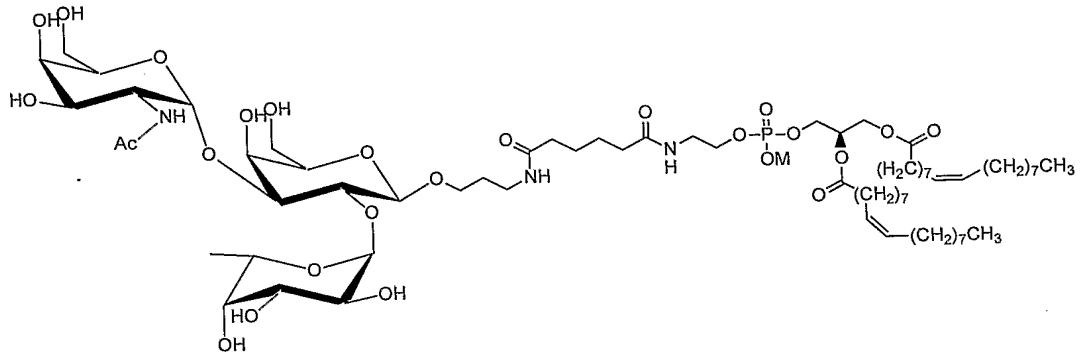
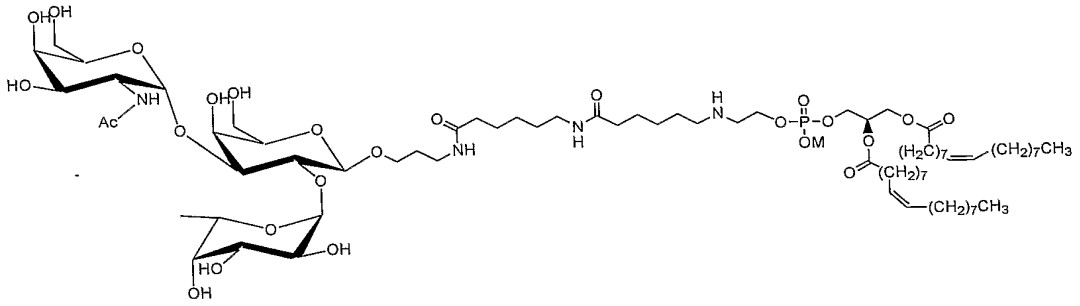
(65) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated A_{tri}-sp-Ad-DOPE (**I**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(66) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated A_{tri}-spsp_1-Ad-DOPE (**II**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(67) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:

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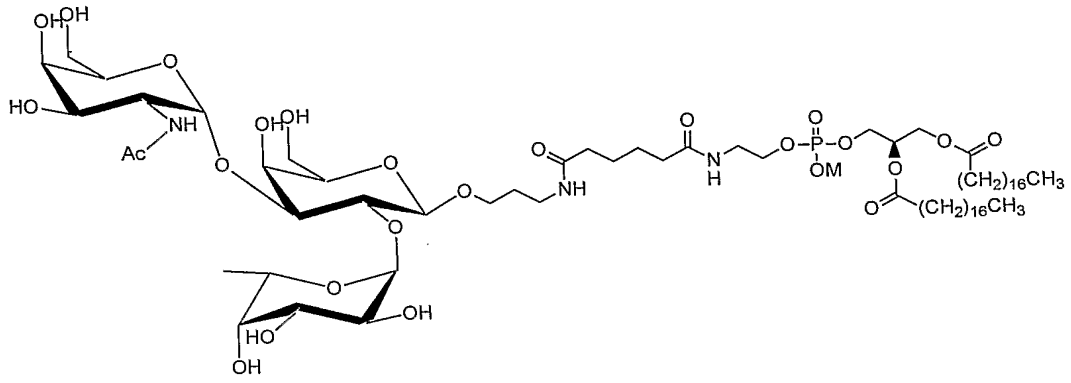
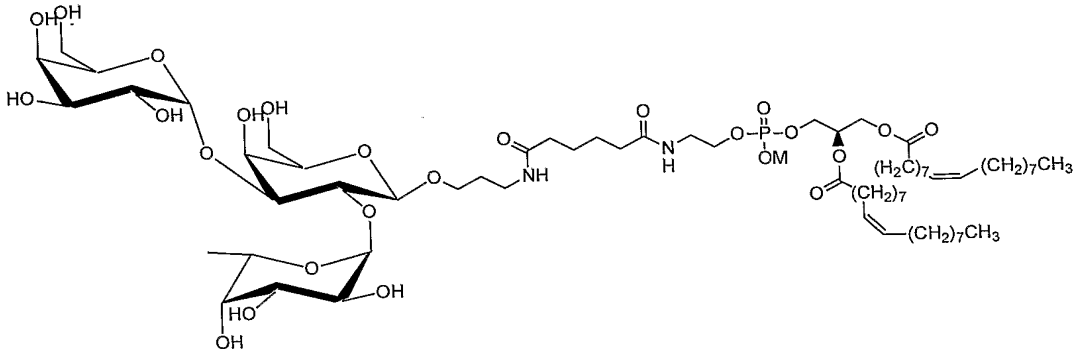


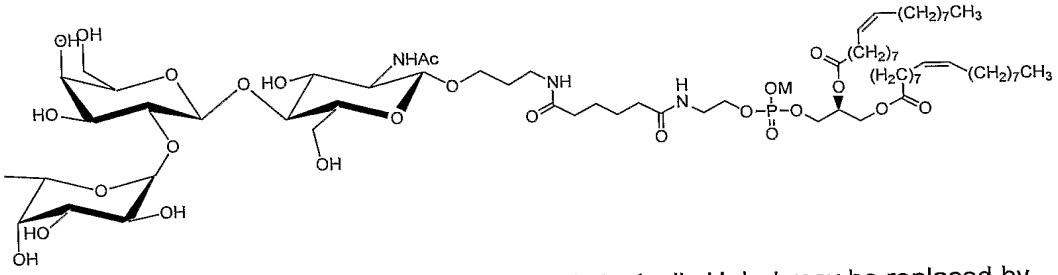
designated A_{tri}-sp-Ad-DSPE (**III**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(68) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated B_{tri}-sp-Ad-DOPE (**VI**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(69) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated H_{tri}-sp-Ad-DOPE (**VII**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(70) The method according to claim 36 where the water soluble synthetic molecule construct

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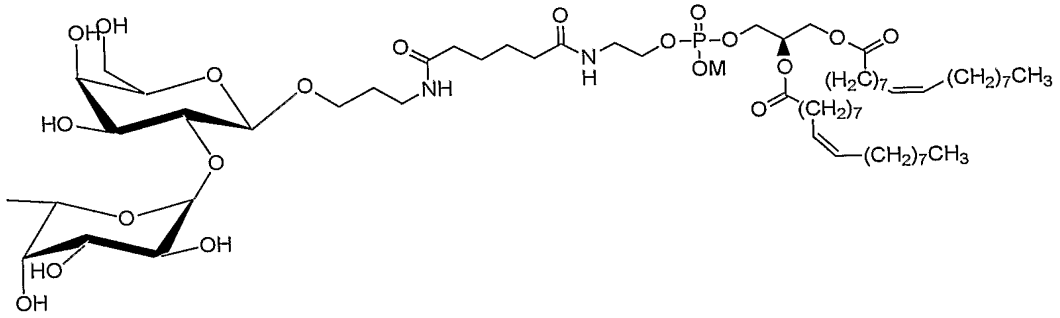
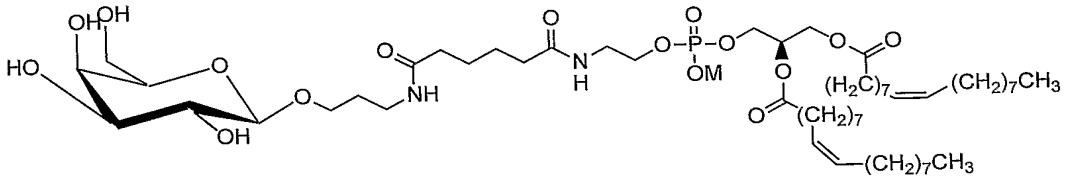
has the structure:



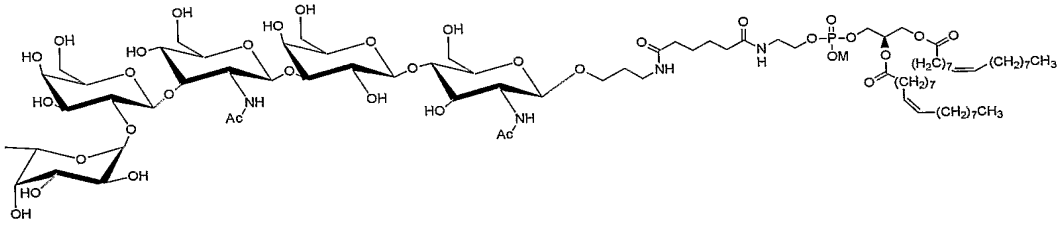
designated H_{di}-sp-Ad-DOPE (**VIII**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(71) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated Galß$_i$-sp-Ad-DOPE (**IX**);

(72) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:



designated Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(73) The method according to claim 36 where the water soluble synthetic molecule construct has the structure:

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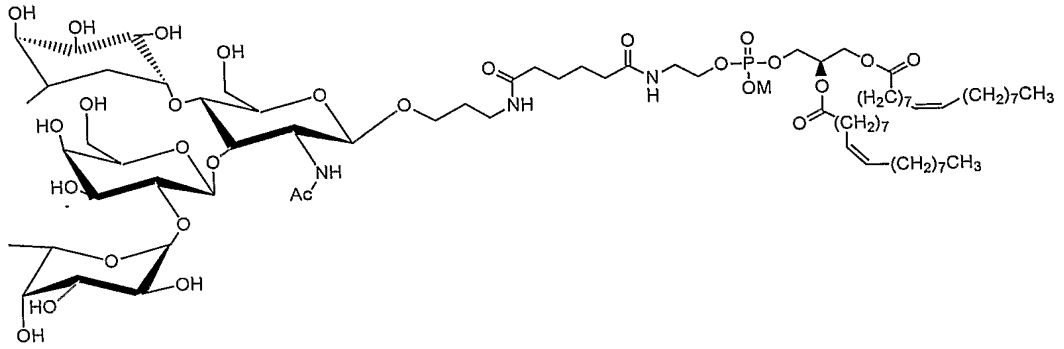

designated Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**) and where M is typically H, but may be replaced by another monovalent cation such as Na^+, K^+ or NH_4^+.

(74) A water **soluble synthetic membrane anchor** or **synthetic molecule construct** prepared by a method according to any one of claims 36 to 73.

(75) A **method** of effecting qualitative and/or quantitative changes in the surface antigens expressed by a cell or multi-cellular structure including the step:

- Contacting a suspension of the cell or multi-cellular structure with a water soluble synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 35 or 74 for a time and at a temperature sufficient to effect the qualitative and/or quantitative change in the surface antigens expressed by the cell or multi-cellular structure.

(76) The method according to claim 75 where the cell or multi-cellular structure is of human or murine origin.

(77) The method according to claim 75 or 76 where the concentration of the water soluble synthetic membrane anchor or synthetic molecule construct in the suspension is in the range 0.1 to 10 mg/mL.

(78) The method according to any one of claims 75 to 77 where the suspension of the cell or multi-cellular structure is contacted with the water soluble synthetic membrane anchor or synthetic molecule construct at a temperature in the range 2 to 37 °C.

(79) The method according claim 78 where the suspension of the cell or multi-cellular structure is contacted with the solution of the water soluble synthetic membrane anchor or synthetic molecule construct at a temperature in the range 2 to 25 °C.

(80) The method according claim 79 where the suspension of the cell or multi-cellular

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structure is contacted with the solution of the water soluble synthetic membrane anchor or synthetic molecule construct at a temperature in the range 2 to 4 °C.

(81) The method according to any one of claims 75 to 80 where F is selected from the group of glycotopes comprising the terminal sugars GalNAcα1-3(Fucα1-2)Galß; Galα1-3Galß; Galß; Galα1-3(Fucα1-2)Galß; NeuAcα2-3Galß; NeuAcα2-6Galß; Fucα1-2Galß; Galß1-4GlcNAcß1-6(Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(Fucα1-2Galß1-4GlcNAcß1-3)Galß; Fucα1-2Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; NeuAcα2-3Galß1-4GlcNAcß1-6(NeuAcα2-3Galß1-4GlcNAcß1-3)Galß; Galα1-4Galß1-4Glc; GalNAcß1-3Galα1-4Galß1-4Glc; GalNAcα1-3GalNAcß1-3Galα1-4Galß1-4Glc; or GalNAcß1-3GalNAcß1-3Galα1-4Galß1-4Glc.

(82) The method according to claim 81 where F is selected from the group of glycotopes consisting of the oligosaccharides GalNAcα1-3(Fucα1-2)Galß and Galα1-3(Fucα1-2)Galß.

(83) The method according to any one of claim 75 or 80 where the synthetic membrane anchor or synthetic molecule construct is selected from the group including: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

(84) The method according to any one of claims 75 to 83 where the cell or multi-cellular structure is an embryo.

(85) The method according to claim 84 where F is an attachment molecule where the attachment molecule has an affinity for a component expressed on the epithelial cells or the extra-cellular matrix of the endometrium.

(86) The method according to claim 85 where the component expressed on the epithelial cells or the extra-cellular matrix of the endometrium can be a naturally expressed component or an exogenously incorporated component.

(87) The method according to any one of claims 75 to 83 where the cell or multi-cellular structure is a red blood cell.

(88) The method according to claim 87 where F is a ligand for a binding molecule where the presence of the binding molecule is diagnostic for a pathological condition.

(89) The method according to claim 88 where F is a ligand for an antibody (immunoglobulin).

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(90) A **cell or multi-cellular structure** incorporating a synthetic membrane anchor or water soluble synthetic molecule construct according to any one of claims 1 to 35 or 74.

(91) The cell or multi-cell structure according to claim 90 where the cell or multi-cellular structure is of human or murine origin.

(92) The cell or multi-cell structure according to claim 90 or 91 where the cell or multi-cell structure is a red blood cell incorporating a water soluble synthetic molecule construct selected from the group including: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

(93) The cell or multi-cell structure according to claim 90 or 91 where the cell or multi-cell structure is an embryo incorporating a water soluble synthetic molecule construct selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

(94) A **kit** comprising a dried preparation or solution of a water soluble synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 35 or 74.

(95) The kit according to claim 97 where water soluble synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 35 or 74 is selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-spsp_1-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_i$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

(96) A **kit** comprising a suspension in a suspending solution of cells or multi-cellular structures according to any one of claims 90 to 93.

(97) The kit according to claim 96 where the suspending solution is substantially free of lipid.

(98) The kit according to claim 96 or 97 where the cell or multi-cellular structure is of human or murine origin.

(99) The kit according to any one of claims 96 to 98 where the cells are red blood cells that do not naturally express A- or B-antigen and incorporate a water soluble synthetic

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molecule construct selected from the group consisting of: A_{tri}-sp-Ad-DOPE (**I**); A_{tri}-$spsp_1$-Ad-DOPE (**II**); A_{tri}-sp-Ad-DSPE (**III**); B_{tri}-sp-Ad-DOPE (**VI**); H_{tri}-sp-Ad-DOPE (**VII**); H_{di}-sp-Ad-DOPE (**VIII**); Galß$_1$-sp-Ad-DOPE (**IX**); Fucα1-2Galβ1-3GlcNAcβ1-3Galβ1-4GlcNAc-sp-Ad-DOPE (**XII**); and Fucα1-2Galβ1-3(Fucα1-4)GlcNAc-sp-Ad-DOPE (**XIII**).

(100) The kit according to claim 99 where the suspending solution additionally contains one or more antibodies.

(101) The kit according to claim 100 where the cells are sensitivity controls.

(102) A **pharmaceutical preparation** comprising a dried preparation or solution of a water soluble synthetic membrane anchor or synthetic molecule construct according to any one of claims 1 to 36 or 74.

(103) The pharmaceutical preparation according to claim 102 where the pharmaceutical preparation is in a form for administration by inhalation.

(104) The pharmaceutical preparation according to claim 103 where the pharmaceutical preparation is in a form for administration by injection.

(105) A **pharmaceutical preparation** comprising cells or multi-cellular structures according to any one of claims 90 to 93.

(106) The pharmaceutical preparation according to claim 105 where the cells or multi-cellular structures are of human or murine origin.

(107) The pharmaceutical preparation according to claim 105 or 106 where the pharmaceutical preparation is in a form for administration by inhalation.

(108) The pharmaceutical preparation according to claim 105 or 106 where the pharmaceutical preparation is in a form for administration by injection.